

## Special Section: Glaucoma

### Dual therapy

# Efficacy, once-daily convenience make drug good choice

## Formulation helps lower IOP when prostaglandin analogue needs add-on

By Cheryl Guttman

Reviewed by John R. Samples, MD

Portland, OR—The novel formulation of timolol maleate 0.5% ophthalmic solution containing potassium sorbate (Istalol, ISTA Pharmaceuticals) is a good option to consider for adjunctive therapy in patients whose IOP is not adequately controlled by a prostaglandin analogue alone, said John R. Samples, MD.

“Compared with other medication choices, timolol provides a greater and more consistent IOP-lowering effect throughout the daytime, and this proprietary preparation of timolol offers the only ophthalmic timolol solution that is approved by the FDA for once-daily administration,” said Dr. Samples, professor of ophthalmology, Casey Eye Institute, Oregon Health & Science University, Portland.

“Based on the work of Brubaker and others, it is well established that beta-blockers don’t work well to lower IOP as well at night; however, they are very effective when used first thing in the morning to blunt the usual pressure rise that many patients experience around the time of awakening,” he said. “Therefore, this once-daily timolol product combined with a once-nightly prostaglandin analogue allows patients who need dual therapy a simple and convenient dosing regimen.”

Incorporation of potassium sorbate in the topical solution enhances the lipophilicity of timolol to increase its penetration through the cornea and into the anterior chamber. As a result, administration of a single drop

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of this timolol formulation in the morning provides effective IOP control around the clock that is equivalent to the IOP-lowering effect of a standard timolol solution administered twice daily.

Dr. Samples noted his opinion that most ophthalmologists probably consider timolol as their first choice for adjunctive therapy with a prostaglandin analogue. However, the results of a recently published meta-analysis provide solid evidence to support that role [van der Valk et al. *Ophthalmology* 2005;112:1177-1185].

Published in a leading peer-reviewed ophthalmology journal, the independent study was conducted by researchers from the department of epidemiology, Maastricht Uni-

versity, The Netherlands, with no industry sponsorship. It pooled data on the IOP-lowering effects of medications evaluated in randomized clinical trials published through 2003.

To be considered for inclusion, papers had to be written in English, German, French, or Dutch, and 85% or more of the study population had to consist of patients with primary open-angle glaucoma or ocular hypertension. Data from evaluations performed after 1 month of treatment were available from 28 studies that included trough effect data for 6,953 participants and peak measurement data for 6,841 individuals.

The non-prostaglandin medications tested were betaxolol, timolol, dorzolamide, brinzolamide, and brimonidine. For both peak and trough measurements, timolol was associated with the greatest mean percent IOP reduction from baseline (–27% and –26%, respectively). Brimonidine had the second greatest IOP-lowering effect at peak

### Take-Home Message

Results of a recent meta-analysis support the use of timolol as the drug of choice for patients needing dual therapy because of uncontrolled IOP with a prostaglandin analogue alone. The novel formulation of timolol maleate 0.5% ophthalmic solution containing potassium sorbate (Istalol, ISTA Pharmaceuticals) is a good option because it is a comfortable and convenient once-daily solution.

(-25%), but was much less efficacious at trough (-18%).

Data from placebo-treated patients showed IOP was lowered by an average of 5% at both peak and trough in the control groups. Effects of the three prostaglandin analogues—latanoprost, travoprost, and bimatoprost—ranged from 31% to 33% at peak and from 28% to 29% at trough. Based on the data, the investigators concluded that the prostaglandin analogues and timolol are the most effective IOP-reducing agents in patients with primary open-angle glaucoma or ocular hypertension.

Dr. Samples noted the novel, once-daily timolol maleate solution may be preferred by some patients over gel-forming preparations that can cause transient blurriness of vision, and while it affords better anterior chamber penetration of timolol than competitor solutions, its use is not associated with an increase in systemic levels of the beta-blocker.

A randomized, double-masked, crossover study investigated that issue in healthy subjects who used the timolol maleate-potassium sorbate solution or a standard timolol solution twice daily for 8 days. In blood samples drawn prior to the morning dose on the eighth day, the mean timolol concentration was significantly lower when patients used the timolol maleate-potassium sorbate preparation compared with the standard formulation, 0.09 versus 0.2 ng/ml, respectively.



Six subjects had detectable levels of timolol after using the sorbate-containing solution compared with seven subjects using the standard timolol solution, and the maximum concentration achieved in any one subject was also lower after continued dosing with the novel formulation compared with the standard, 0.28 versus 0.69 ng/ml, respectively.

“A few things should be kept in mind when reviewing these data,” Dr. Samples noted. “First, the timolol maleate-potassium sorbate solution was administered using an exaggerated dosing schedule rather than the

recommended once-a-day regimen, and it still resulted in less systemic absorption.

“In addition, however, these data should remind ophthalmologists there is a real potential for systemic exposure in patients using ophthalmic beta-blockers. Therefore, all of the contraindications to beta-blockers still need to be respected when prescribing this timolol solution. Nevertheless, it may be a safer choice in marginal situations when there are minor relative contraindications to beta-blocker use or in terms of reducing the risk of other potential systemic side effects associated with this class of medications,” Dr. Samples said.

He also noted that if one is going to use a beta-blocker, using an agent such as this one, which has published data that suggest an improved safety profile over generic timolol solutions, seems like the best approach. ◻

## FYI

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